

Definition

Urea and creatinine are nitrogenous end products of metabolism. Urea is the primary metabolite derived from dietary protein and tissue protein turnover. Creatinine is the product of muscle creatine catabolism. Both are relatively small molecules (60 and 113 daltons, respectively) that distribute throughout total body water. In Europe, the whole urea molecule is assayed, whereas in the United States only the nitrogen component of urea (the blood or serum urea nitrogen, i.e., BUN or SUN) is measured. The BUN, then, is roughly one-half (28/60 or 0.446) of the blood urea.

The normal range of urea nitrogen in blood or serum is 5 to 20 mg/dl, or 1.8 to 7.1 mmol urea per liter. The range is wide because of normal variations due to protein intake, endogenous protein catabolism, state of hydration, hepatic urea synthesis, and renal urea excretion. A BUN of 15 mg/dl would represent significantly impaired function for a woman in the thirtieth week of gestation. Her higher glomerular filtration rate (GFR), expanded extracellular fluid volume, and anabolism in the developing fetus contribute to her relatively low BUN of 5 to 7 mg/dl. In contrast, the rugged rancher who eats in excess of 125 g protein each day may have a normal BUN of 20 mg/dl.

The normal serum creatinine (^3Cr) varies with the subject's body muscle mass and with the technique used to measure it. For the adult male, the normal range is 0.6 to 1.2 mg/dl, or 53 to 106 $\mu\text{mol/L}$ by the kinetic or enzymatic method, and 0.8 to 1.5 mg/dl, or 70 to 133 $\mu\text{mol/L}$ by the older manual Jaffé reaction. For the adult female, with her generally lower muscle mass, the normal range is 0.5 to 1.1 mg/dl, or 44 to 97 $\mu\text{mol/L}$ by the enzymatic method.

Technique

Multiple methods for analysis of BUN and creatinine have evolved over the years. Most of those in current use are automated and give clinically reliable and reproducible results.

There are two general methods for the measurement of urea nitrogen. The diacetyl, or Fearon, reaction develops a yellow chromogen with urea, and this is quantified by photometry. It has been modified for use in autoanalyzers and generally gives relatively accurate results. It still has limited specificity, however, as illustrated by spurious elevations with sulfonylurea compounds, and by colorimetric interference from hemoglobin when whole blood is used.

In the more specific enzymatic methods, the enzyme urease converts urea to ammonia and carbonic acid. These products, which are proportional to the concentration of urea in the sample, are assayed in a variety of systems, some of which are automated. One system checks the decrease in absorbance at 340 nm when the ammonia reacts with α -ketoglutaric acid. The Astra system measures the rate of

increase in conductivity of the solution in which urea is hydrolyzed.

Even though the test is now performed mostly on serum, the term *BUN* is still retained by convention. The specimen should not be collected in tubes containing sodium fluoride because the fluoride inhibits urease. Also chloral hydrate and guanethidine have been observed to increase BUN values.

The 1886 Jaffé reaction, in which creatinine is treated with an alkaline picrate solution to yield a red complex, is still the basis of most commonly used methods for measuring creatinine. This reaction is nonspecific and subject to interference from many noncreatinine chromogens, including acetone, acetoacetate, pyruvate, ascorbic acid, glucose, cephalosporins, barbiturates, and protein. It is also sensitive to pH and temperature changes. One or another of the many modifications designed to nullify these sources of error is used in most clinical laboratories today. For example, the recent kinetic-rate modification, which isolates the brief time interval during which only true creatinine contributes to total color formation, is the basis of the Astra modular system.

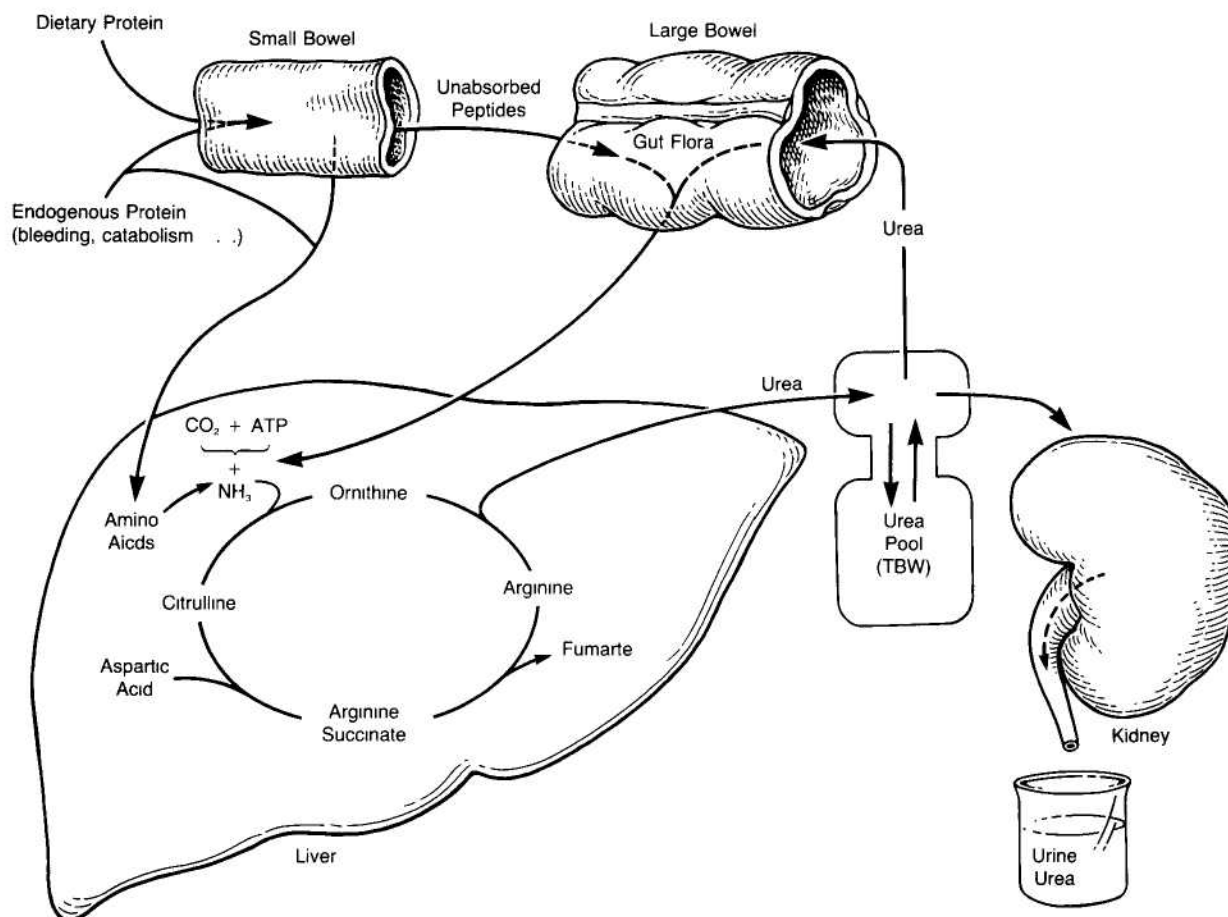
More specific, non-Jaffé assays have also been developed. One of these, an automated dry-slide enzymatic method, measures ammonia generated when creatinine is hydrolyzed by creatinine iminohydrolase. Its simplicity, precision, and speed highly recommend it for routine use in the clinical laboratory. Only 5-fluorocytosine interferes significantly with the test.

Creatinine must be determined in plasma or serum and not whole blood because erythrocytes contain considerable amounts of noncreatinine chromogens. To minimize the conversion of creatine to creatinine, specimens must be as fresh as possible and maintained at pH 7 during storage.

Basic Science

More than 99% of urea synthesis occurs in the liver. Its primary source is dietary protein. In the gut, the protein is converted into peptides and amino acids, more than 90% of which are absorbed and carried to the liver. In the hepatocyte, the amino acids are deaminated and transaminated. The resulting excess nitrogen feeds into the urea cycle to be incorporated into urea. The protein moieties escaping absorption by the small bowel, plus recycled urea, are converted into ammonia by gut flora predominantly in the colon. The ammonia diffuses through the portal circulation into the liver to enter the urea cycle (Figure 193.1).

The amount of urea produced varies with substrate delivery to the liver and the adequacy of liver function. It is increased by a high-protein diet, by gastrointestinal bleeding (based on plasma protein level of 7.5 g/dl and a hemoglobin of 15 g/dl, 500 ml of whole blood is equivalent to 100 g protein), by catabolic processes such as fever or in-

**Figure 193.1**

Absorption, metabolism, and excretion of urea. (Modified from Raforth and Onstad, 1975.)

fection, and by antianabolic drugs such as tetracyclines (except doxycycline) or glucocorticoids. It is decreased by low-protein diet, malnutrition or starvation, and by impaired metabolic activity in the liver due to parenchymal liver disease or, rarely, to congenital deficiency of urea cycle enzymes. The normal subject on a 70 g protein diet produces about 12 g of urea each day.

This newly synthesized urea distributes throughout total body water. Some of it is recycled through the enterohepatic circulation. Usually, a small amount (less than 0.5 g/day) is lost through the gastrointestinal tract, lungs, and skin; during exercise, a substantial fraction may be excreted in sweat. The bulk of the urea, about 10 gm each day, is excreted by the kidney in a process that begins with glomerular filtration. At high urine flow rates (greater than 2 ml/min), 40% of the filtered load is reabsorbed, and at flow rates lower than 2 ml/min, reabsorption may increase to 60%. Low flow, as in urinary tract obstruction, allows more time for reabsorption and is often associated with increases in antidiuretic hormone (ADH), which increases the permeability of the terminal collecting tubule to urea. During ADH-induced antidiuresis, urea secretion contributes to the intratubular concentration of urea. The subsequent buildup of urea in the inner medulla is critical to the process of urinary concentration. Reabsorption is also increased by volume contraction, reduced renal plasma flow as in congestive heart failure, and decreased glomerular filtration.

Creatinine formation begins with the transamidation from arginine to glycine to form glycoylamine or guani-

doacetic acid (GAA). This reaction occurs primarily in the kidneys, but also in the mucosa of the small intestine and the pancreas. The GAA is transported to the liver where it is methylated by S-adenosyl methionine (SAM) to form creatine. Creatine enters the circulation, and 90% of it is taken up and stored by muscle tissue. In a reaction catalyzed by creatine phosphokinase (CPK), most of this muscle creatine is phosphorylated to creatine phosphate. Each day, about 2% of these stores is converted nonenzymatically and irreversibly to creatinine (Figure 193.2).

Thus, creatinine production essentially reflects lean body mass. Because this mass changes little from day to day, the production rate is fairly constant. Absolute creatinine production declines with age in line with decreasing muscle mass. Unlike urea, creatinine is largely unaffected by gastrointestinal bleeding or by catabolic factors such as fever and steroids. However, the ingestion of cooked meat can raise the ^{54}Cr because cooking converts the creatine in meat to creatinine. Certain drugs, notably the psychoactive phenacemide, can increase the production rate.

Like urea, creatinine distributes throughout total body water. Its concentration in serum is a function of the usually constant production and excretion rates. It may be slightly higher in the evening than in the morning, due most likely to dietary meat intake by day.

In normal subjects, creatinine is excreted primarily by the kidneys. There is minimal extrarenal disposal or demonstrable metabolism. As a small molecule (molecular weight of 113 daltons), it is freely filtered by the glomerulus.

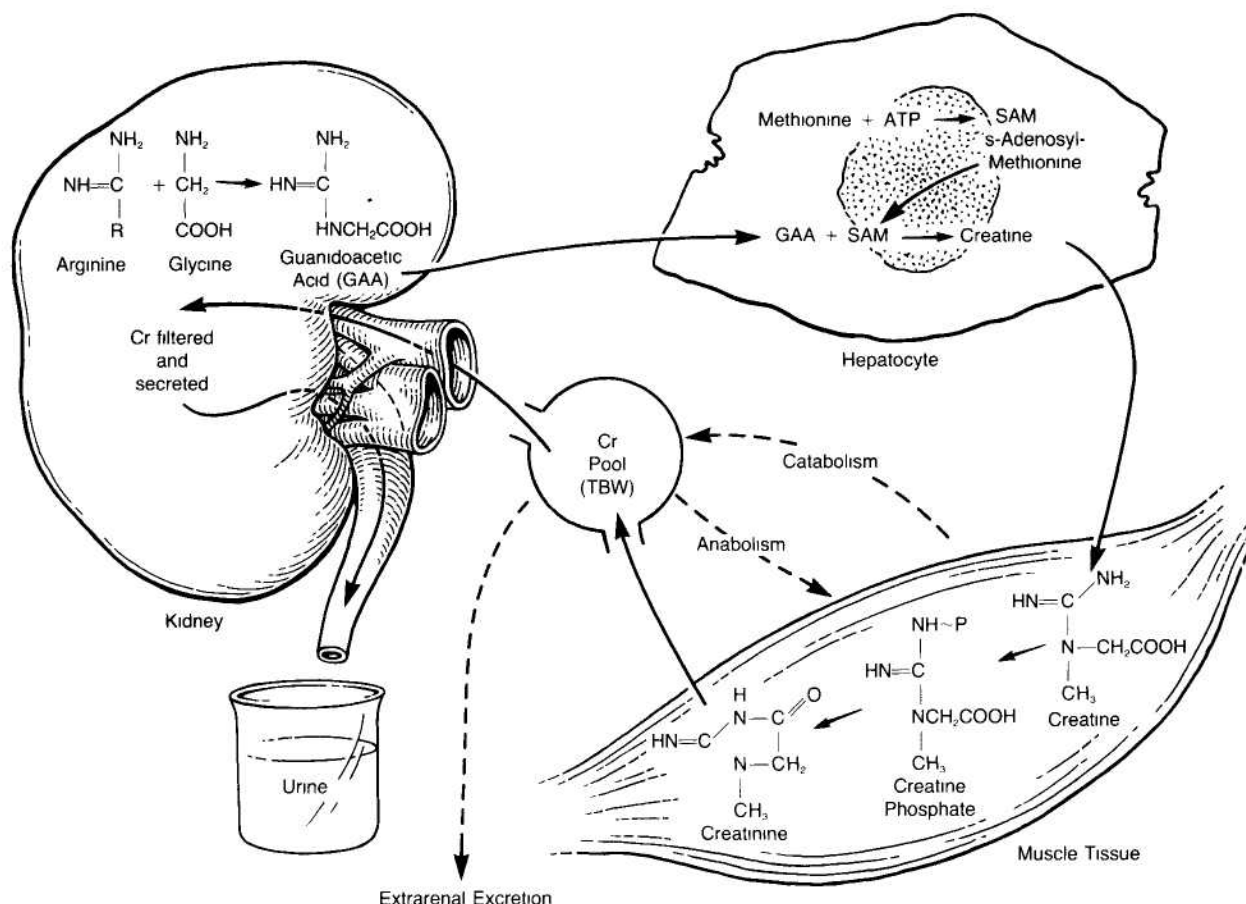


Figure 193.2
Metabolism and excretion of creatinine. (Modified from Dosseter, 1966.)

Unlike urea, it is not reabsorbed or affected by urine flow rate. It is normally secreted by the tubules in a small but significant amount (up to 10% of total excretion). Excretion of both urea and creatinine is increased during exercise without producing significant change in serum concentration. The total creatinine excretion in a normal man averages 14 to 26 mg/kg/day, and in a normal woman 11 to 20 mg/kg/day. Excretion declines with age, and is about 10 mg/kg/day in a 90-year-old man. However, it should not vary more than 10 to 15% in a given individual. The amount excreted has been used as a rough index of the completeness of daily urine collection.

Measurement of urine creatinine excretion is used in calculating the creatinine clearance ($^{\circ}\text{Cr}$). Short of the more precise but technically impractical inulin clearance, the $^{\circ}\text{Cr}$ is the standard clinical tool for estimating GFR, especially in the early stages of renal disease. In that setting $^{\circ}\text{Cr}$ and BUN are not very useful indices of GFR due to their parabolic relationship and to the wide range of normal (Figure 193.3).

In contrast, the $^{\circ}\text{Cr}$ has the major disadvantage of inaccuracies in urine collection, especially during short-term clearances or in patients with low urine volumes. For this reason, 24-hour clearances are preferred for general use, because the usually larger volumes will minimize errors of collection. The concentration of creatinine in the serum and urine is determined, and with careful attention to the units of measurement, the $^{\circ}\text{Cr}$ is calculated as follows:

$$^{\circ}\text{Cr} = \frac{^{\text{u}}\text{Cr} V}{^{\text{s}}\text{Cr}}$$

where $^{\text{u}}\text{Cr}$ = urine creatinine concentration in mg/dl, V = urine volume in ml/min, and $^{\text{s}}\text{Cr}$ = serum creatinine concentration in mg/dl. The result may then be standardized to 1.73 m² body surface area (BSA).

The subject's BSA is related to weight and height and is usually obtained from a nomogram. Example:

$$\text{Urine volume} = 1080 \text{ ml/day} = \frac{1080}{24 \times 60} \text{ or } 0.75 \text{ ml/min}$$

$$^{\text{u}}\text{Cr} = 90 \text{ mg/dl}$$

$$^{\text{s}}\text{Cr} = 1.2 \text{ mg/dl}$$

$$\text{Weight} = 75 \text{ kg}$$

$$\text{BSA} = 1.5 \text{ m}^2$$

$$^{\circ}\text{Cr} = \frac{^{\text{u}}\text{Cr} V}{^{\text{s}}\text{Cr}} = \frac{90 \text{ mg/dl} \times 0.75 \text{ ml/min}}{1.2 \text{ mg/dl}}$$

$$= 56 \text{ ml/min}$$

$$\frac{^{\circ}\text{Cr}}{1.73 \text{ m}^2} = 56 \times \frac{1.5}{1.73}$$

$$= 48.6 \text{ ml/min/1.73 m}^2$$

Several shortcuts to estimate the $^{\circ}\text{Cr}$ without collecting urine have been proposed. The earliest and probably the least accurate ignores the subject's age and weight, and simply divides 100 by the $^{\text{s}}\text{Cr}$. The Cockcroft-Gault formula is the one usually recommended for use in calculating dosage

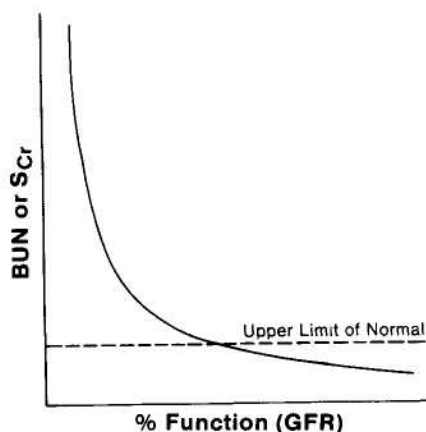


Figure 193.3

Relationship of blood urea nitrogen or serum creatinine to glomerular filtration rate.

of drugs (especially nephrotoxic antibiotics). It takes into account the well-documented fall in GRF with age as follows:

$$^{\circ}\text{Cr} = \frac{(140 - \text{age}) \times (\text{body weight, kg})}{72 \times ^{\circ}\text{Cr}(\text{mg/dl})}$$

In advanced renal failure, net creatinine excretion decreases significantly. Even though tubular secretion increases as GFR falls, it does not compensate for the decrease in filtration when the GFR is below 50 ml/min/1.73 m². Further, there is measurable creatinine metabolism by gut flora and, in some patients, decreased creatinine synthesis. Thus ^cCr is unreliable and often overestimates GFR in chronic renal failure and in cirrhosis. It has been suggested that, when the GFR is below 15 ml/min, the mean of ^cCr plus urea clearance gives a more accurate index of GFR. Thus:

$$\text{GFR} = \frac{^{\circ}\text{Cr} + ^{\circ}\text{Urea}}{2}$$

Certain drugs may affect ^cCr without changing GFR. Salicylates, cimetidine, and trimethoprim interfere with tubular secretion of creatinine and cause a spuriously low ^cCr.

Clinical Significance

The BUN and ^sCr are screening tests of renal function. Because they are handled primarily by glomerular filtration with little or no renal regulation or adaptation in the course of declining renal function, they essentially reflect GFR. Unfortunately, their relation to GRF is not a straight line but rather a parabolic curve (Figure 193.3). Their values remain within the normal range until more than 50% of renal function is lost. Within that range, however, a doubling of the values (e.g., BUN rising from 8 to 16 mg/dl or ^sCr from 0.6 to 1.2 mg/dl) may mean a 50% fall in the GFR. Therefore, in the early stages of renal disease, these tests could create a false sense of security. Random values above the midrange of normal should be corroborated by a normal ^cCr before one can confidently tell a patient that his or her kidney function is normal.

At the other end of the curve, small changes in kidney function can produce large increments in BUN and ^sCr.

Here, these tests are generally adequate to follow a patient's course. Indeed, the reciprocal of the ^sCr plotted against time shows a straight-line progression of renal disease in each individual patient, and can be used to predict the advent of end-stage renal disease.

At all stages of renal insufficiency, the ^sCr is a much more reliable indicator of renal function than the BUN because the BUN is far more likely to be affected by dietary and physiologic conditions not related to renal function (Table 193.1). For example patients with congestive heart failure and intact kidneys commonly present with a BUN of 50 to 70 mg/dl and an ^sCr below 1.2 mg/dl. Of course, ^sCr may rise under some of these extrarenal factors, but seldom will it exceed 3 to 4 mg/dl. The stages of renal failure have been defined according to the ^sCr as follows:

^s Cr 2.5 to 4.9	Moderate renal failure
5 to 9.9	Severe renal failure
10 or greater	End-stage renal disease

With so many limitations on the usefulness of the BUN, one wonders why the test survives. When taken with the ^sCr, it is a very useful clue to the presence of a prerenal or postrenal component to azotemia. Other factors being normal, a patient with an ^sCr of 5.0 mg/dl would be expected to have a BUN close to 50 mg/dl. If the BUN is 100 mg/dl instead, then the clinician should begin a search for extrarenal factors (Table 193.1). Note that this 10 to 1 ratio applies best in moderate to advanced renal failure. Attention to these reversible complications of uremia can give a patient a reprieve from an untimely sentence of end-stage renal disease.

A low BUN/Cr ratio suggests inadequate protein intake, reduced urea synthesis as in advanced liver disease, supernormal excretion of urea as in sickle cell anemia, increased creatinine production as in rhabdomyolysis, or more effective removal of urea than creatinine during dialysis.

The BUN survives and is finding wide application in the nutritional management of critically ill patients. The urea nitrogen appearance (UNA) objectively lets the intensivist know whether the patient's nitrogen needs are being met. The UNA assessment requires the measurement of BUN at the beginning and end of the period of observation as well as the total urea excretion.

Table 193.1

Extrarenal Factors Affecting BUN and ^sCr

Factor by mechanism	BUN	^s Cr
Increased substrate		
High protein intake	↑	→ or sl ↑
Gastrointestinal bleeding	↑	→
Catabolic states (fever, steroids, burns, etc.)	↑	→
Rhabdomyolysis	↑	↑ ↑
Decreased substrate		
Malnutrition	↓	→
Starvation	↓	→
Hypoperfusion		
Dehydration	↑	→
Congestive heart failure	↑	→
Shock	↑	→
Diminished blood volume (GI bleeding)	↑	→
Urinary tract obstruction	↑	→

Key: ↑ = increase, ↓ = decrease, → = no change.

$$\text{UNA (g/day)} = \text{urinary urea N (g/day)} \\ + \Delta \text{ body urea N (g/day)}$$

where

$$\Delta \text{ body urea N} = (\text{BUN}_f - \text{BUN}_i) \times 0.6 \times \text{BW}_f \\ + (\text{BW}_f - \text{BW}_i) \times \text{BUN}_f \times 1 \text{ and} \\ \text{BW} = \text{body weight in kilograms}$$

The BUN and creatinine, taken together, are valuable screening tests in evaluating renal disease. Though they may fall short as absolute indicators of renal function at any given point in time, they are useful in following progression of disease.

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